National Institute of Allergy and Infectious Diseases

NIAID Council News

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President Clinton's FY 1999 Budget—A Bonanza for Biomedical Research

NIAID director Dr. Anthony S. Fauci relayed the good news to Council: the President's FY 1999 budget calls for unprecedented funding increases for NIH as part of a "21st Century Research Fund."

The President's FY 1999 budget requests $1.15 billion more for NIH than we received in FY 1998.

Then, a funding rise of 50 percent over the next five years will boost the NIH budget to more than $20 billion by 2003.

The FY 1999 increase will drive the Institute's success rate to 40.5 percent, up from 36.3 percent in FY 1998.

Meanwhile, our FY 1998 payline (the funding cutoff point) is set at the 24 percentile for non-AIDS and 26 for AIDS.

In future years, NIAID expects to continue to succeed in vying for research dollars relative to other institutes.

One of the reasons, as Dr. Fauci told Council, is that much of our research falls in NIH director Dr. Harold Varmus' special emphasis areas.

Within the President's FY 1999 budget, Dr. Varmus plans to put aside $652 million for these research areas and also for improvements in research infrastructure.

The goal is to increase success rates for investigator-initiated applications, beef up training programs, and help integrate new technologies into NIH-supported labs.

Further, Dr. Varmus wants to spend another $35 million on the Shared Instrumentation and Biomedical Research Support programs of the National Center for Research Resources and $23 million on extra-

continued on page 20

Inside

INITIATIVES & funding

New NIAID Training Opportunities

To build a bigger base of research training, NIAID and NIH have embarked on several innovative training initiatives. They feature creative new award types and even a "portable grant."

The new training opportunities hit several targets: one award helps postdocs make a smooth transition to assistant professor, others train clinical researchers in patient-oriented research, and still more awards expand courses and careers in research ethics.

A unique new award creates a portable grant, allowing a postdoc to apply before finding a sponsoring institution.

Postdoc transition to assistant professor award

NIAID has created a brand new grant type: the Research Scholar Development Award (K22) to support outstanding postdocs making their way to their first academic position as an assistant professor.

The award is unique in that it allows the grantee to apply before having a sponsoring institution, earning the distinction as the first portable NIH grant.

Intended strictly to provide start-up monies, the award gives you two years of nonrenewable support.

Grantees receive $150,000 in direct costs in the first year and $100,000 in the second year, with flexibility on how the money is spent.

After the application is reviewed, a candidate with a fundable score will have one year to "shop" for an assistant professor position.

Awards will not be automatic but will depend on NIAID's assessment of the sponsoring institution's commitment to the grantee in his or her new role.

New awards for clinical investigators

To address a shortage of scientists conducting patient-oriented research, NIH is opening up new opportunities for physician-scientists.

Although NIH supports a large number of M.D.s, most conduct basic research.

With the new crop of awards, NIH hopes to bolster the number of M.D.s conducting patient-oriented research (see boxes at right and on next page).

New awards in research ethics

As part of President Clinton's apology to the survivors and relatives of participants in the Tuskegee Syphilis Study, NIH developed two new programs to help prevent this type of lapse in ethics from recurring.

In November, NIH announced two program announcements, one to develop research ethics courses and the other to support candidates interested in pursuing careers in research ethics.

The Short-Term Courses in Research Ethics PA provides institutions with monies to create instruction for students in biomedical, behavioral, and public health fields.

It also provides travel and per diem funds for students to

New NIAID-Only Training Award

Research Scholar Development Award (K22)

Supports outstanding postdocs making their way to a first academic position as an assistant professor.

attend the courses. Under the T15 award, grantees may develop, offer, or evaluate ethics courses ranging from three days to six weeks long.

Courses address the ethical, legal, and social implications of research conducted in people.

Topics may include research design, the handling of special populations, informed consent, and privacy.

Mentored scientist development award in research ethics

The Mentored Scientist Development Award in Research Ethics develops professional bioethicists who will serve as a resource for the research community. To apply, you must have a doctorate in a research or health-related field and be willing to commit at least 75 percent of your effort to career development in research ethics.

This K01 award supports training in research ethics for health professionals working at academic and other health-related institutions in biomedical, behavioral, or public health research, particularly research involving human participants. It includes a mentored experience in research ethics.

For more information about applying for either award, call Dr. Milton Hernandez, director of the Office of Science Training, at 301/496-3775.

Also, go to the *NIH Guide for Grants and Contracts* for the full announcements.

The Mentored Scientist Development Award in Research Ethics is at <*http://www.nih. gov/grants/guide/pa-files/PAR-98-006.html*>, and Short-Term Courses in Research Ethics is at <*http://www.nih.gov/grants/guide/pa-files/PAR-98-005.html*>.

NIAID is administering both awards, which are cosponsored by CDC, Health Resources and Services Administration, and Agency for Health Care Policy and Research.

More training news: higher stipend levels

Stipends for many NRSA pre- and postdoctoral trainees went up in FY 1998, and another 25 percent increase is in the President's budget for FY 1999. FY 1998 stipend levels are on the Web at *http://www.nih.gov/grants/guide/1998/98.01.09/n1.html*>.

Try NIAID's new training line

If you are looking for basic information on training grants (T32), fellowships (F), career development (K) awards, and Research Supplements for Underrepresented Minorities (RSUM), or you do not know which grant type is for you, call us at

800/380-3876

You will access a brief description of training programs with an option of being connected to an NIAID training staff member.

NIH announced two new awards in research ethics: one to train research ethicists, the other to create courses.

New NIH Patient-Oriented Training Grants

Institutional Curriculum Award (K30)

This training grant-like award supports training for clinicians interested in patient-oriented research.

Clinical Investigator Award (K08)

This award supports clinicians in basic or patient-based research.

Mentored Patient-Oriented Research Career Development Award (K23)

This new mechanism supports clinicians after specialty training.

Mid-Career Investigator in Patient-Oriented Research Award (K24)

This award supports senior-level clinicians so they can mentor younger M.D.s.

Rounds Two and Three for HIV Vaccine Innovation Grants

The Innovation Grant Program for Approaches in HIV Vaccine Research began its second cycle with a new program announcement featuring the same advantages as the previous one: a shorter application format and accelerated award and review.

Based on advice from NIAID's AIDS Vaccine Research Committee, the new PA seeks applications in two scientific areas: 1) the structure and immunogenicity of the HIV envelope protein, and 2) studies of T-cell responses in lentiviral disease. Applications were due on March 10, 1998, but more is yet to come.

Look for three new receipt dates and the ability to apply in other research areas.

Hold tight for round three!

The Institute is already planning the next iteration of the Innovation Grant Program, with more investigator-pleasing changes on tap.

First, the program will use the three AIDS receipt dates standard for the Center for Scientific Review (CSR), providing more opportunities to apply.

Second, the program will be broadened to any area of AIDS vaccine research, instead of the current limitation to two or three areas per receipt date.

Peer review will shift to CSR with the advent of the new, more vaccine-receptive AIDS study sections (see the article on page 7 for more information).

Targeting your application to one of the committee-identified priority areas still has advantages. Investigators applying in these areas may receive special consideration that would make it easier to get funded.

Check the Web

A few months before each receipt date, we will post information on the areas the committee is seeking out on our new AIDS Vaccine Research Web site at <*http://www.niaid.nih.gov/daids/vaccine/default.htm*>.

How Successful Is NIAID's Shift to PAs?

The extramural research community lauded NIAID's move toward publishing more PAs and fewer RFAs two years ago when we made this major policy switch.

Though most experts felt we were going in the right direction, we now have enough data to show just what kind of impact the shift has made.

NIAID leadership looked at the numbers at NIAID's January Winter Program Review.

Since the first PAs appeared two years ago, the payline has jumped from the 10 percentile for non-AIDS and 14 for AIDS to 24 for non-AIDS and 26 for AIDS.

Applicants benefited from a higher success rate: 34 percent of applications responding to the new PAs were funded

As a result, it is considerably easier for investigators who send us an unsolicited application to get funded.

One of the questions surrounding the new policy has been: Would PAs stimulate research in high-priority areas?

Investigators responded vigorously

Happily, the community has responded to the new PAs with gusto.

In response to our 48 PAs active as of March 3, 1998, we received 1,250 applications. More than 90 percent of the applications were new, compared to the NIH

norm of 70 to 75 percent (the rest were amended applications), and many were from new investigators as well.

Further, we received 200 fewer amended applications while the overall number of applications remained the same.

Applicants benefited from a higher success rate too: we funded 34 percent of the PA-responding applications.

Though most funded applications had ratings within the payline, a significant number had percentiles beyond the cutoff due to the importance of the research.

Pointing to another measure of success, more than 50 percent of applicants queried said the PA was a significant factor in focusing the topic of their application.

Reconsideration of the three-year expiration

At the last Winter Program Review, managers reevaluated the PAs' three-year expiration date.

Some PAs have already met their goals; for example, the Modern Vaccines for Measles and Mycoses PA has been readvertised as addressing mycoses only, having stimulated enough measles research.

Thus, we may terminate PAs after a gap has been filled and automatically close them after two years. Such changes will be announced in the NIH *Guide*.

DAIT Plans New RFAs in Immunology

NIAID's Division of Allergy, Immunology, and Transplantation recommends keeping an eye out for two important new requests for applications, one for program centers in immunology and the other a fast-track grant program for accessing patients and patient tissue from clinical trials to study immune-related topics.

Human Immunology Centers of Excellence

This RFA invites applications for program project grants for interactive, synergistic studies of the basic mechanisms regulating human immune responses.

Of primary interest are multidisciplinary programs to define clinically relevant genetic, biochemical, cellular, and systemic parameters of human immunity and tolerance.

The receipt date is October 23, 1998. For more information, contact Dr. Helen Quill, chief, Basic Immunology Branch, DAIT, 301/496-7551 or e-mail Helen_Quill@nih.gov.

Mechanistic studies in clinical trials RFA has bold new features

Working with other institutes, NIAID is taking the lead in an RFA for mechanistic studies in clinical trials of immunomodulatory interventions for immune system diseases.

The RFA has two unique features to help investigators capitalize on information generated by clinical trials of immune diseases.

First, the RFA allows you to piggyback onto existing clinical trials to access patients or patient materials, resources that allow you to evaluate the mechanisms of the intervention, disease activity, therapeutic effect, and immune system function.

Second, NIAID is collaborating with the Center for Scientific Review on a hyper-accelerated review and award that will fund these grants in as little as 13 weeks after the application receipt date.

NIH will accept applications on an ongoing basis with the receipt date on the 9th of each month, beginning October 9, 1998.

Applications received by the 9th of the month will be reviewed at the next available review meeting.

NIH news

How First-Time Applicants Can Succeed After the R29 Phase-Out

Since NIH eliminated the R29 (FIRST award) for new investigators last November, some questions have arisen about the transition to end First Independent Research Support and Transition Awards (R29).

Like their experienced counterparts, most new applicants seeking a research project grant will apply for an R01 grant using the PHS 398 application kit.

Though you still have the option of applying for a FIRST award, you may not want to because the R29 is being phased out.

Special features for new applicants

To limit the possibility of newcomer disadvantage, NIH has committed to supporting at least the same number of new investigators as it did last year, even if that means spending more money on the awards.

Further, NIH will be changing the face page of the PHS 398 application to enable new applicants to identify themselves by checking a special box.

NIH is still working on that change, which will signal peer reviewers that the applicant is less experienced and may have less preliminary data than would a veteran grantee.

Until the May receipt date, applicants still have the option of using R29s but may not want to, considering that they are being phased out.

Options for current R29 applicants

If you have already submitted an R29 application and did not receive a fundable score, you have three options:

- Submit an amended R29.
- Submit an amended application as an R01.
- Make substantial changes and submit the application as a new R01.

Each alternative has different requirements. When sending NIH an amended R29, include an introduction describing in detail the changes you made in response to the reviewers' critiques; also include letters of recommendation.

But if you are sending in an amended application as an R01, include an introduction but no letters of recommendation.

If you choose to submit a new application, give it a new title, and do not include an introduction. NIH would treat this as an entirely new application.

In contrast, amended applications retain their identification number, with an "A1" or "A2" tag, and summary statements from the previous review are read by reviewers (according to standard NIH procedures).

For more help, call your program officer and read the policy announcement in the *Guide* at *<http://www.nih.gov/grants/guide/1997/97.11.21/n1.html>*.

NIH Extends Large Grant Policy

On March 12, NIH updated its policy for large grants.

The requirement of application preacceptance that formerly applied only to new grants now applies to all unsolicited applications, including continuing (type 2) grants.

Investigators submitting applications requesting more than $500,000 or more for any year must 1) contact the institute that would fund the application before writing it and 2) get agreement in writing that the institute will consider the application for an award.

For more information, contact your program officer and read the announcement in the *Guide* at *<http://www.nih.gov/grants/guide/1997/97.11.21/n1.html>*.

NIH Reorganizes AIDS SRGs, Vaccine Study Section to Come

CSR has merged its former eleven AIDS Scientific Review Groups into eight new ones, with minimal effect on the review of NIAID applications.

The main change was adding study sections to accommodate the move of the National Institute on Drug Abuse and National Institute on Mental Health to NIH.

The committee heading the effort included two NIAID staffers, Drs. Carl Dieffenbach and Polly Sager from the Division of AIDS.

At focus groups held with the research community, NIH learned that there is very strong support to keep an AIDS scientific review group, the umbrella organization for the study sections.

Investigators said they were afraid that breaking up the SRG would have a negative effect as has occurred in countries such as the Netherlands, England, and Germany.

New names, familiar topics

New study sections are similar to old ones. NIAID's applications will be reviewed in primarily five study sections (see box at right).

NIH is finalizing the changes, and information should be on the Web around the time this newsletter is published.

Check the NIH home page at <*http://www.nih.gov/*> and the CSR home page at <*http://www.csr.nih.gov/*> for more information.

Applicants are strongly encouraged to self-refer to NIH (see the article in our May 1997 newsletter issue at <*http://www.niaid.nih.gov/ncn/nl5-97.pdf*>).

Vaccine study section in the works

CSR is planning a new special emphasis panel that will review applications for vaccine studies for all infectious diseases in the areas of translational research, concept development, and testing. Earlier, basic vaccine-related immunology will still be reviewed in ARRN.

Moving in response to recommendations from the Levine Panel and National Vaccine Advisory Committee, NIH hopes the new study section will encourage applications as well as communication and cross-fertilization in the field.

New CSR AIDS Study Sections

ARRM—Molecular and Cellular Biology of HIV (formerly Virology, ARRC)

ARRN—Immunology and Pathogenesis of HIV (formerly Immunology, ARRA)

ARRO—Therapeutics Discovery and Development (formerly Drug Development, ARRD)

ARRP—AIDS-Associated Complications (Opportunistic Infections and Cancer) (formerly OIs, ARRE)

ARRR—Epidemiologic and Clinical Studies of HIV/AIDS (formerly Epidemiology, ARRB)

Plus three less applicable to NIAID

ARRQ—Basic AIDS Neuropathogenesis and Co-Morbidity Factors

ARRS—Behavioral and Social Science 1

ARRT—Behavioral and Social Science 2

CSR Successfully Uses NIAID's Electronic Review System

The Tropical Medicine and Parasitology study section of the Center for Scientific Review is finishing up its trials of NIAID's ground-breaking electronic peer review system to see whether the electronic format can universally benefit review organizations and applicants.

NIAID recently asked the TMP reviewers to evaluate their experience using our review system. Thus far, the data show the almost universal appeal of electronic initial peer review. Of the 16 (out of 20) reviewers responding to our request, 15 recommended using the system (see graphics below).

One reviewer commented, "I can't see going back to doing the reviews the old way."

More than 80 percent of respondents felt the electronic system was easy to use and enhanced the discussion; all felt it helped them resolve divergent scores.

One reviewer summed up the feeling by saying, "I can't see going back to doing reviews the old way."

Reviewers valued having time to review applications before the meeting and read each other's comments. These changes give them more time to digest an application's strengths and weaknesses and focus feedback to applicants.

This feature is especially useful in resolving scores with wide discrepancies among reviewers.

TMP chair Dr. Phil LoVerde told us, "The system as it stands is excellent. Reviewers have the opportunity to see each other's reviews and make adjustments or firm up their arguments to support their positions."

Having access to others' critiques before the meeting emerged as one of the most significant benefits, by helping reviewers focus their thoughts. Thus, by the time they meet face-to-face, reviewers have already had a chance to absorb each other's comments.

Dr. Marilyn Parsons' comment was typical. "I feel the most important part was being able to read the second reviewer's review and think about the points raised. Then I was able to see whether I was off the mark or felt the other reviewer needed to consider other ideas."

The premeeting period was productive for discussing points of disagreement or those needing clarification among reviewers. With those items out of the way, meeting time was spent synthesizing major points of feedback for applicants.

"The system allowed a more thoughtful consideration of difficult or controversial points," noted Dr. Dyann Wirth.

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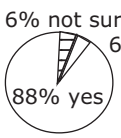
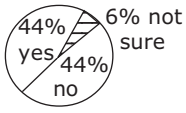
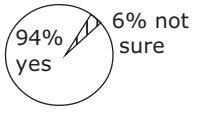
Reviewers Like Electronic Review



Did access to critiques before review lead to a more informed discussion?



Did availability of critiques alter how you scheduled time for reviews?



Would you recommend using this system in other study sections?

Viewing Comments and Scores*

100% Discordant scores identified applications with issues needing resolution.

80% I felt more comfortable triaging applications.

68% I gained an overall sense of the quality of the review.

50% Discussions were shorter on most agreed-to points.

* Percentage of reviewers who agreed

INSTITUTE & staff

Staff Changes: Dr. John La Montagne and Dr. John McGowan

Two of NIAID's key staff members, Dr. John R. La Montagne and Dr. John J. McGowan, have changed places following the departure of Dr. Lawrence R. Deyton, former acting director of the Division of Extramural Activities (DEA).

Continuing as coeditor of this newsletter, Dr. McGowan returns to his previous role as DEA director.

Replacing him as NIAID deputy director is Dr. La Montagne, former director of the Division of Microbiology and Infectious Diseases (DMID). Dr. La Montagne has long been a leading figure in the Institute.

After coming here in 1976 as influenza program officer, he was asked by Dr. Fauci to jump start the Division of AIDS as its first director in 1985. In 1987, Dr. La Montagne became DMID director, where he led many key Institute efforts. The most recent include overseeing the successful completion of international pertussis vaccine trials, for which he received a Presidential Meritorious Executive Rank Award, and providing leadership to the Multilateral Initiative on Malaria Research.

Dr. La Montagne received his Ph.D. in microbiology from Tulane University in 1971. Following graduation, he moved to the University of Pittsburgh to work in the laboratory of Dr. Julius Youngner on the properties of viral particles produced by persistent infections caused by Newcastle disease virus.

Having left the Institute in December, Dr. Deyton is now director of HIV/AIDS Services and Research at the Department of Veterans Affairs. He is also serving as an NIAID *ex officio* Council member representing that agency.

NIH News—*continued from page 8*

CSR Uses NIAID's Electronic Review

Eleven respondents felt the electronic format afforded them a better perspective of the quality of the application and its review, and 14 of 16 felt more comfortable triaging applications than they did in a traditional review setting.

In addition to electronic review, TMP has been testing three other reinvention experiments: applicant self-referral, delayed IRB approval submission, and tie-in to Council expedited review.

We queried reviewers on the first two, and results were positive. Fourteen reviewers liked having the option of sending in an abbreviated amended application (two were unsure).

The vast majority felt that delaying submission of IRB approval had little effect on the review discussion time or the ability to assess fitness to conduct the research.

New NIH Policy: Including Children in Clinical Trials

On March 6 NIH announced that children must be included in NIH-supported and -conducted clinical research, barring a scientific or ethical reason not to do so.

The new policy stems from concerns voiced by Congress and the pediatric research community that only a small fraction of drugs and biological products have included children in clinical trials, and a majority of marketed drugs are not labeled for use in children.

NIH hopes the new guidance will increase participation of children in clinical research.

For more information, see the NIH *Guide* at *<http://www.nih.gov/grants/guide/notice-files/not98-024.html>*.

Unraveling the Lifestyle of *Legionella pneumophila*: Research of NIAID's Newest Presidential Early Career Award Recipient, Michele Swanson, Ph.D.

Dr. Swanson is exploring the molecular interactions that determine the fate of microbes in macrophages, using *Legionella pneumophila* as a model system.

She hypothesizes that the organism has one set of virulence factors that move it out of harm's way from degradative lysosomes in macrophages and another *modus operandi* for establishing a replication niche.

Dr. Swanson's work links growth conditions and virulence to explain how the pathogen adapts and persists in different environments.

Progress has been made on two fronts. As a postdoctoral fellow, Dr. Swanson developed fluorescence microscopic techniques to analyze the fate of *L. pneumophila* in macrophages.

More recently, her lab has discovered a phenotypic switch that may allow this pathogen to adapt to changing environments.

Sabotaging the host cell

Dr. Swanson's work strives to unlock a secret of *L. pneumophila* pathogenesis: its ability to evade phagosome-lysosome fusion.

Understanding this process has major health implications. Several organisms, including *Mycobacteria, Chlamydia,* and *Toxoplasma*, flourish because they are not degraded by lysosomes after internalization into macrophage phagosomes.

Dr. Swanson isolated growth-defective mutants of *L. pneumophila* and then used microscopy to track the intracellular progress of the wild-type and mutant strains.

Fluorescence and electron microscopic studies showed that virulent *L. pneumophila* replicates in a specialized vacuole surrounded by the host endoplasmic reticulum.

After uptake by macrophages, *L. pneumophila* evaded phagosome-lysosome fusion, replicating in the ER-associated compartment. Cell lysis occurred in about 24 hours.

In contrast, a slow-growing mutant that associates poorly with the ER offered genetic evidence of the necessity of the specialized vacuole.

This work underscores the critical role of the intracellular pathway in maintaining virulence. Because macrophages orchestrate immune responses, this work also has broad implications for understanding many other diseases and biological functions.

Replicative form, virulent form

L. pneumophila inhabits not only alveolar macrophages and amoebae, where it replicates, but also lives as a free-living parasite. Further work by Dr. Swanson's lab links growth conditions and virulence to explain how the pathogen adapts and persists in different environments.

Dr. Swanson has shown how *L. pneumophila* transforms from a replicative form early in infection into a virulent form when nutrient levels decline.

In these studies, the replication-phase *L. pneumophila* were sodium-resistant, lacked flagella, were noncytotoxic, and failed to evade macrophage lysosomes.

However, this phenotype changed dramatically during the post-growth phase when the infectious bacteria, cultured in broth, became cytotoxic, sodium-sensitive, and flagellated.

Further, the pathogens acquired the ability to evade degradation by macrophage lysosomes during the latter phase.

This developmental change was in direct response to nutrient levels. *L. pneumophila* expressed its

virulent phenotype in response to starvation. Conversely, when nutrients were plentiful, the organism exhibited its replicative phenotype.

Confirming the correlation of these traits, a mutant defective for growth in macrophages isolated by Dr. Swanson failed to convert from the replicative to the virulent form when starved.

Such phenotypic changes appear to be the pathogen's blueprint for survival. When nutrients are plentiful, *L. pneumophila* replicates; when nutrients are limited, it expresses virulence factors that let it lyse cells, disperse in the environment, and reestablish itself in a new host.

Additional experiments indicate that similar events likely occur *in vivo.*

After *L. pneumophila* has replicated inside a macrophage vacuole, bacterial density increases while nutrient levels decline.

This ultimately forces the pathogen to lyse the cell and find a new home.

Council Delves Into Research Ethics

A research ethics discussion at the February Council meeting highlighted issues bearing on future therapeutic and vaccine trials in developing countries. Former Council member Barry Bloom, Ph.D., of the Albert Einstein College of Medicine led with a presentation following up on his paper published in *Science* in January.

A long-standing NIAID grantee and MERIT awardee, Dr. Bloom wrote that differences in ethical vantage points between the developed and developing worlds are raising new ethical questions yet to be answered by international guidelines.

Differences in standards of care in developed and developing countries make it hard to determine what is appropriate and ethical when conducting research in the developing world.

For example, if people in a poor country become HIV-infected during a vaccine trial, who would pay for the cost of our "standard of care" (which may not be standard anywhere else anyway)?

Dr. Bloom doubted whether international research would be possible if investigators had to uphold U.S. standards of care worldwide.

At Council, he explored the dilemmas and debate surrounding recent trials in the Third World testing AZT to prevent maternal-infant HIV transmission.

The controversy brought to light ambiguities in international guidelines, creating major headaches for investigators and policy makers alike.

Two sets of international ethics guidelines are the most influential: the Helsinki Declaration of 1964 and the International Guidelines for Biomedical Research Involving Human Subjects.

The latter are produced by the Council for International Organizations of Medical Sciences (CIOMS) to clarify the Helsinki guidelines and relate particularly to research in developing countries.

Building on the success of ACTG 076

At center stage in the recent ethics debate are trials of AZT to curb maternal-fetal HIV transmission.

These studies are controversial partly because standard care available in the countries of study differs from standard care here, and our standard is simply not feasible in the developing world.

Differences in standards of care in developed and developing countries make it hard to determine what is appropriate and ethical for research in the developing world.

The phase II trials are testing AZT in pregnant mothers using a much simpler and more realistic

regimen than the one made standard practice in the U.S. by ACTG 076.

Preliminary results show a 50 percent reduction in HIV transmission using this regimen (see the *Morbidity and Mortality Weekly Report*, March 6, 1998, for more information).

The ACTG 076 regimen could not be used because it is too technically demanding, requiring the delivery of AZT to the mother five times a day for 11 weeks before and 11 weeks after birth, intravenous AZT during delivery, and AZT to the infant for 6 weeks. In addition, mothers do not breast feed.

There are ongoing discussions to clarify the wording in the relevant guidelines mandating the use of "best proven treatment" in clinical trials.

Criticism of the studies of a simplified approach has centered on the use of a placebo control, which is the equivalent of standard care in many developing countries and permits direct comparison of the new regimen with the current standard.

The goal of these studies was to find a regimen that would curb maternal-fetal HIV transmission and could actually be adopted as standard medical care.

Dr. Bloom stated he felt that "most everyone believes the trials were motivated by doing good."

Though economics is not ethics, as Dr. Bloom emphasized, economic factors are important in countries such as Uganda, engulfed by an overwhelming AIDS problem but so poor that it spends only $6 a year per person on health care.

Problems for vaccine research

Ethical issues will surely confront investigators embarking on research of HIV vaccines.

Two key problems in supporting vaccine trials in a developing country are a lack of clarity on what medical care researchers from developed countries are obligated to provide and the proscription in the international guidelines against conducting phase I trials in underdeveloped areas.

NIAID has long been grappling with such questions.

Dr. Bloom recalled early Council discussions when concerns emerged that if people in vaccine trials did not change their behavior they could increase their risk of becoming infected.

"We understood the risk, and I think the Institute has been very responsive in getting that kind of information and seeking and respecting it," he said.

Clearer international guidelines would simplify matters for the Institute and the researchers it supports.

As Council member Dr. Jerrold Ellner said, "It would be so

Two new awards in research ethics

NIH now supports two ethics-specific awards.

Short-Term Courses in Research Ethics (T15)

Funds institutions to develop or sponsor ethics courses. For details, see the *Guide* announcement at <http://www.nih.gov/grants/guide/pa-files/PAR-98-005.html>.

Mentored Scientist Development Award in Research Ethics (K01)

Supports candidates interested in pursuing careers in research ethics. Applicants must have a doctorate and commit at least a 75 percent effort to career development in research ethics. Go to the *Guide* at <http://www.nih.gov/grants/guide/pa-files/PAR-98-006.html> for more information.

much better for all of us if guidelines were developed rather than our being asked to defend individual trials and designs."

Best treatment or appropriate treatment?

There are ongoing discussions to clarify the wording in the relevant guidelines mandating the use of "best proven treatment" in clinical trials.

When taken to an extreme, this concept is often untenable for studies in developing countries.

For example, a study of aspirin or beta blockers to prevent heart disease would have to provide either angioplasty or coronary artery bypass as alternative treatments.

The American Medical Association has asked the World Medical Association to consider revising the Helsinki document by changing "best proven treatment" to "appropriate treatment."

They believe this would help clarify the dilemma of what to do when the best proven treatment is unclear.

Further, an organ of the United Nations coordinating that agency's AIDS efforts, called UNAIDS, is actively addressing bioethical issues.

UNAIDS will hold a series of meetings to discuss the complex issues surrounding international research.

Striving to build a consensus, it is holding a series of meetings with health officials from around the world, hearing views on such questions as whether changing to "appropriate treatment" would work.

It will then meet in June to pick the best ideas and concerns and bring them to CIOMS to help focus possible revisions.

There is also pressure to change the guideline advising against involving people from underdeveloped communities in phase I and II trials.

AIDS investigators here and in developing countries see this guideline as a hindrance to studies in countries where raging epidemics can give rapid answers to research questions.

And representatives from developing countries have been outraged at being excluded from phase I and II studies.

Dr. Ezekiel Emanuel, director of the Department of Clinical Bioethics, NIH Clinical Center, and member of the President's Advisory Committee on Bioethics, commented that the Helsinki and the CIOMS regulations have been revised almost every four to five years and should be considered as living documents.

Council member Dr. Robert Couch agreed that it "really is important that ethics evolve, and guidelines should never be rigid."

Online Drug Discovery Resources

NIAID's Division of AIDS has a new online listing of the drug discovery resources it supports together with the program staff person to contact for more information.

You can find the *Preclinical Development of AIDS Resource Guide* on the Web at <*http://www.niaid.nih.gov/daids/PDATguide/overview.htm*>.

The Institute funds a wide range of resources that can provide valuable support to researchers in drug development, including:

- Databases
- Screening systems
- *In vitro* drug testing for anti-HIV activity
- AIDS animal models
- Chemistry and pharmaceutical support
- Preclinical safety assessment of experimental therapeutics
- Immunologic evaluations
- Clinical laboratory technologies

Council Subcommittee Wowed by Technology Presentations

At the meeting of the Division of Allergy, Immunology, and Transplantation (DAIT) Council subcommittee in February, DAIT treated subcommittee members to a special technology session, part of NIAID's continuing effort to promote new technology development and use for immunology research.

Called "Innovative Scientific Approaches for the Study of Cellular and Molecular Processes," the program featured Drs. Mark Davis of Stanford University, Linda Griffith and Lisa Steiner of the Massachusetts Institute of Technology, and Scott Fraser of the California Institute of Technology.

Staining T cells, building tissue

Coming from very different backgrounds, each speaker presented the latest technologies in his or her areas and showed how these innovations could further immunology research.

Dr. Davis unveiled the latest applications of his system for staining antigen-specific T cells from peripheral blood of humans or mice.

This technique lets investigators track and determine the frequencies of T cells responsive to any antigen/MHC combination, providing a powerful way to assess the cellular immune responses following antigen exposure or vaccination.

Then, Dr. Griffith presented her work growing three-dimensional tissue *in vitro* by providing a polymer scaffold and a system for perfusion of tissue with microvasculature.

The more immediate applications for this technology include *in vitro* screening of drugs and reagents to assess effects on tissues, with the long-term goal of growing organs *in vitro*.

From imaging to zebrafish

New frontiers in imaging were portrayed by Dr. Fraser, who uses magnetic resonance imaging and two-photon microscopy to track cell movement and development *in vivo* in real time.

His new reagents for staining cells enable him to follow the progression of virtually any cell in live mice and other small rodents. Adapting this technology to humans is a long-range pursuit already under way.

Finally, Dr. Steiner talked about using zebrafish to study immune system development. The ability to easily manipulate this vertebrate genetically makes it a powerful tool for studying genes affecting immune system development and possibly function.

This session furnished Council with a sampling of emerging technologies that could be applied to immunology research. Council members then explored how NIAID could bolster its efforts to bring these technologies to its investigators and the need for further investment.

We are continuing efforts to expand information to immunologists and are considering programs to make emerging technologies more readily available to our research community.

NCSA Biology Workbench Online

The NCSA Biology Workbench <*http://biology.ncsa.uiuc.edu*> gives you rapid access to biological databases and analysis tools.

This new approach to biology software and data access is particularly valuable for instruction and also for use in the developing world.

Developed by the University of Illinois at Urbana-Champaign, the site houses more than a hundred public domain programs in genomics and protein analysis seamlessly linked to the worldwide genome and protein databases.

Data translation and programming are invisible to the user, and there is a built-in tutorial on the site.

FEATURE articles

NIAID in Front Lines of Hong Kong Flu Crisis

When the "bird flu" crisis took hold in December, the world turned to NIAID to furnish the weapons needed to launch the attack against H5N1. Drawing on our reserves of resources and expertise, the Institute moved quickly.

Within a few days (see timeline on page 17), we sent avian flu expert and longtime NIAID grantee Dr. Robert Webster to Hong Kong, awarded a contract to develop a vaccine, and provided CDC and WHO with the only antiserum in existence to type the strain.

Dr. Webster shared some of his experiences at the February Council meeting to which he was invited as an *ad hoc* Council member.

At Council, Dr. Fauci commended the effort as "another example of having done work years ago that is spelling our ability to move very quickly."

He also commented that "it was imperative that H5N1 be detected and treated before the regular flu season begins in March."

Meeting the flu challenge mobilized NIAID's program, grants, and contracts staff who, within one week, identified scientific resources, coordinated arrangements with CDC and the State Department, and awarded a grant and a contract.

Though several people in Hong Kong had contracted H5N1 earlier last year, the crisis became full blown in December, with two new cases and one death.

Altogether, there were 18 confirmed cases, six fatal.

The ominous part was that the outbreak marked the first time an avian strain infected people, who have no immunity to it.

In previous jumps to humans, the virus was reassorted in an intermediate host, usually pigs, which provided the "melting pot" for getting the bird genes into a strain that infects humans.

NIAID's Initial Actions to Counter "Bird Flu"

Awarded grant supplement to conduct animal surveillance and isolate the virus to Dr. Robert Webster.

Provided antiserum for diagnostic typing to WHO Influenza Collaboration Centers and U.S. state laboratories.

Provided H5 hemagglutinin as a reagent in serological screening, immunogenicity, and efficacy studies in chickens.

Awarded a contract to Protein Sciences Corporation for production of recombinant H5 hemagglutinin vaccine.

Submitted a vaccine clinical protocol for IRB review and FDA approval.

A mission possible

NIAID has a long history of support of flu research, including H5N1, first isolated in August 1997.

The Institute maintains the world's only typing reagents, needed to diagnose patients and define strains for vaccines.

When the crisis arose, we sent 600 vials of these reagents to

CDC and WHO collaborative centers in the U.S. and abroad and another 20 vials to FDA.

Fortunately, NIAID also supports one of the world's foremost experts on flu, Dr. Webster, who works at St. Jude's Research Hospital in Memphis Tennessee.

As soon as the crisis emerged, Dr. Webster was ready to go.

After arriving in Hong Kong, he conducted animal surveillance and isolated H5N1 and other avian influenza viruses.

He also studied the role of animals other than chickens in transmission and looked for a nonpathogenic strain that could be used in a vaccine.

International team identified sources

Dr. Webster's international team identified the sources of H5N1, an effort made possible by a supplement to his NIAID grant.

While in Hong Kong, he got a good look at how birds are housed there, methods that can contribute to the emergence of new epidemics.

For example, cages holding different types of birds are often stacked upon each other, facilitating the exchange of body fluids and excrement.

He recommended changes to authorities in Hong Kong and hopes more permanent changes will prevent further outbreaks such as this one.

Dr. Webster told Council that the killing of the 1.5 million chickens in December was critical. He also described the flu response as a "tremendous collaborative effort on the part of NIH, CDC, and WHO. By going there and acting very rapidly, we may have shut the door on this pandemic," he said.

"By going there and acting very rapidly, we may have shut the door on this pandemic."

However, he cautioned us not to be complacent, "We cannot sit on our hands and say we have been successful."

Back home, Dr. Webster continues to characterize the avian viruses, while CDC is working on the human strains.

Producing a vaccine in record time

In December, NIAID awarded a contract to Protein Sciences Corporation of Meriden, Connecticut, to produce 1,000 doses of recombinant H5 hemagglutinin vaccine.

Within three weeks, the company produced a single lot of vaccine to be used in a clinical trial of at-risk lab and public health workers, with further production anticipated.

Without the unique expertise of this company, there would have been formidable obstacles to overcome.

There were no reagents for H5, and USDA prohibits shipping the virus because it is lethal to poultry.

Further, difficulties in growing the Hong Kong H5N1 isolate in eggs suggested that creating a vaccine would be far from simple.

But Protein Sciences had an edge from previous work developing recombinant HA antigens and vaccines successfully tested in chickens and people in NIAID-sponsored trials.

Its technology allowed fast expression of the HA gene from the first Hong Kong case and then production of a recombinant vaccine.

The vaccine consists of purified recombinant hemagglutinin monovalent type A (A/Hong Kong/157/97) H5 in a baculovirus expression vector in serum-free *Spotoptera fugiperda* insect cells.

Protein Sciences is also producing H5 hemagglutinin to be used as a reagent for screening and immunogenicity studies in chickens and production of antisera in sheep.

Vaccine begins for lab workers; grantees can also qualify

With the goal of protecting lab workers from a potentially lethal virus, the vaccine represents a

handsome payoff from NIAID's investment in this area of research.

Beginning in February, NIAID began recruiting participants into the trial.

The protocol involves immunizing at-risk personnel using a two-dose regimen with three weeks between the first and second dose. This design resulted from discussions with PIs and other experts based on experience in former trials.

A dosing trial will also take place at an NIAID Vaccine Treatment and Evaluation Unit to learn the optimum dose and spacing between doses. The trial will immunize lab workers at five sites: the NIH Clinical Center, FDA, CDC, USDA, and St. Jude's, plus possibly sites in Hong Kong, England, and Japan.

People working with H5N1 under an NIH grant can also be immunized.

NIAID had supported previous clinical trials of influenza A subtypes H3 and H1HA in five studies of 552 subjects. These studies showed the recombinant HA vaccine to be safe and immunogenic in young and elderly adults.

Hong Kong "Bird Flu" Chronology

EVENTS		RESPONSES
1997		
First case reported	**May**	
Second case reported	**November 7**	
Third and fourth cases	**Late November**	
Second death	**December 6**	
	August	**Typing sera** developed with NIAID funds identifies first case.
	December 9	**NIAID makes available HA_0 H5 hemagglutinin** to CDC, FDA, USDA and for screening chickens.
	December 9	**NIAID sends typing sera** for diagnostic kits for WHO and U.S. state health agencies.
	December 17	**NIAID awards grant supplement** to Dr. Webster.
	December 19	**NIAID awards contract** to PSC for 1,000 units of vaccine.
1998		
	January 5	**NIAID submits vaccine protocol** for NIH IRB approval.
	January 13	**NIAID files IND with FDA** for vaccine trial.
	January 20	**HA_0 H5 vaccine vials filled**; PSC submits vaccine master file to FDA.
	February 4	**PSC ships vaccine to NIAID repository** for distribution to clinical sites.
	February 11	**FDA approves vaccine protocol.**

NIAID Launches Frontal Attack on Staph

With the daunting specter of emerging vancomycin-resistant *Staphylococcus aureus* (SA), NIAID is planning a major offensive to fend off a potentially devastating menace to public health.

The February DMID Council subcommittee meeting endorsed bold new Institute plans while approving two grants to sequence the SA genome.

Reduced vancomycin-susceptible SA (VISA) is cropping up in various parts of the world as the organism becomes incrementally more resistant.

The process is hardly new: SA had become completely resistant to penicillin by the late 1950s, and was developing resistance to methicillin by the late 1970s. Vancomycin was left as the sole effective drug to treat methicillin-resistant SA.

But vancomycin's reign may be ending. Strains isolated in Japan in 1996 and in Michigan and New Jersey last year had intermediate-level resistance. And most scientists feel that full resistance to vancomycin is simply a matter of time.

In light of the seriousness of the problem, NIAID brought together what it called a "consultation" group of experts headed by Dr. Gordon Archer, chairman, Division of Infectious Diseases, Virginia Commonwealth University.

At the September 22 meeting in Bethesda, the group suggested steps the Institute should take to address drug resistance, which led to a new plan and initiatives.

This critical effort will further benefit from additional funds Dr. Fauci donated from his director's reserve, a move he announced at February Council.

Panel recommendations

Hold state-of-the-art conference on VISA: delve into identification, characterization, and clinical significance; pathogenesis; vaccines and other preventions; resistance mechanisms; and strategies to limit the spread of resistant organisms.

Establish research networks: study incidence and prevalence of VISA (including screening of banked isolates), pathogenesis, drug resistance, infection control and antibiotic use restrictions; create study group.

Fund sequencing of genome.

Make CDC isolates available by mail to PIs.

Expand research on SA and resistance.

SA "consultation" recommends more research

Including scientists from academia, CDC, and FDA, the consultation group came up with a series of recommendations, many of which NIAID is already implementing, including building a network for investigators, funding sequencing projects, and boosting research.

Basic recommendations (see box below) endorse research on the mechanisms of pathogenesis, development of diagnostics and vaccines, enhancement of research collaborations, and conduct of a state-of-the-art conference on VISA research issues.

Consensus was strong on the need for better collaboration, and NIAID is already putting together the components of a new SA research network.

The group felt that now may be an auspicious time to set up a network. So far VISAs have shown up individually, and though colonies are less sensitive, they are emerging slowly so there is still time to react.

After approval at last Council, NIAID funded two grants to sequence a methicillin-sensitive reference strain of the SA genome and a well-studied strain that is methicillin-resistant. The group felt more information is

needed on the phenotypes of VISA strains to determine whether they are arising in patients and whether they are new or simply newly detected.

However, detection is no small problem. In the studies of three VISA strains, CDC scientists Drs. Theresa Smith, Michael Lancaster, and Fred Tenover reported that disc diffusion did not pick up the VISA phenotype.

To enhance detection capability, the group recommended developing a gold standard test for use by clinical microbiology labs.

The CDC investigators also presented data suggesting that studies of VISA colonies may be a productive avenue for further research. In their work, VISA colonies showed intriguing correlations: slow growth correlated with reduced virulence, and small colony size and thickened cell walls with heightened resistance.

These findings led the group to recommend increasing research of SA colonization to develop a vaccine, design ways to interfere with attachment, or colonize the host with less virulent organisms.

For vaccine research, the group advised pursuing approaches targeting SA attachment proteins or their ligands and antitoxin vaccines involving superantigens.

On a more administrative note, the panel unanimously recommended that CDC's VISA isolates should be available through the mail. CDC agreed, and you can request them from Dr. Tenover.

Group seeks increased support

As NIAID's SA program officer Dr. Stephen Heyse told the group, the Institute's portfolio has 22 R01s and R29s as well as several training, small business, and career development awards.

Despite our support of more than 100 grants relevant to antibiotic resistance, the group wanted to see more due to the global threat of SA.

Meanwhile, the two new sequencing grants will provide invaluable information to the research community. Dr. Steven Gill of The Institute for Genomic Research plans to publish the genome on the Web and will also make available small insert plasmid lambda clone sets upon request. Dr. John J. Iandolo of Oklahoma University Health Sciences Center Department of Microbiology and Immunology is the PI on the other SA sequencing award.

Though the SA genome has been sequenced three times by pharmaceutical companies, the information is proprietary. With a two-year goal of getting the full genome (99 percent after one year), the group felt the investment was well worth it.

Also, six new small business innovation research (SBIR) grants were awarded this year concerning some aspect of SA or antibiotic resistance.

Network: sharing resources, information

With the first parts expected to be in place this year, the Network for Research on SA (NARSA) will give basic and clinical investigators a common reference for discussing the organism and access to the same research strains.

The network will enhance communications and facilitate not only basic research on pathogenesis but also future multicenter studies. Plus, NIAID plans to set up a Web site for the network to facilitate information sharing.

Because the organisms are hard to detect, they may be much more common than we currently know. Sharing isolates through a network will help find VISAs previously undetected. NARSA will support electronic information sharing and meetings, will integrate with CDC's surveillance system on antibiotic resistance, and will support a case registry and repository of isolates.

Find the NARSA RFP at <*http://www.nih.gov/grants/guide/notice-files/not98-043.html*>, and check the concept on the *Council News* Web site at <*http://www.niaid.nih.gov/ncn/conmid-f.htm*>.

The RFP supports the infrastructure for a network of basic scientists, clinical microbiologists, and clinical investigators to characterize clinical strains of VISA and, ultimately, conduct epidemiologic studies and clinical trials of interventions.

Through the contract, strains will be made available at no charge to grantees. The network will help standardize methods to determine sensitivity and resistance, and eventually link centers for multicenter trials.

FY 1999 Budget—

continued from page 1

mural construction. Meanwhile, the President's budget builds in $90 million for construction of the new NIH Clinical Research Center, $126 million for other NIH infrastructure, and $9.1 million for the new Vaccine Research Center (adding to the $19.5 million allotted for FY 1998).

Dr. Fauci assured Council that NIAID would continue its long-standing policy of targeting most of the budget increase to research project grants (e.g., R01s).

In contrast, Intramural continues its decline relative to the budget despite the funds for the Vaccine Research Center.

NIAID *Council News*

Editors

Maya Hadar, Managing Editor
John J. McGowan, Science Editor

Editorial Board

Patricia Baron, DAIDS
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Hortencia Hornbeak, DEA
Gregory Milman, DAIDS
Vicki Seyfert, DAIT

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Send correspondence to:

Maya Hadar
Managing Editor, **NIAID *Council News***
National Institutes of Health
National Institute of Allergy and Infectious Diseases
Division of Extramural Activities
Solar Building, Room 3C22
9000 Rockville Pike
Bethesda, MD 20892

NIAID *Council News*
National Institutes of Health
National Institute of Allergy and Infectious Diseases
Division of Extramural Activities
Solar Building, Room 3C22
9000 Rockville Pike
Bethesda, MD 20892

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